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A Review on Solid Self Micro-emulsifying Drug Delivery System: A Method for Enhancement of Oral Bioavailability

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ABSTRACT

Nearly 40% of new drug candidates possess low aqueous solubility, which is a challenge in development of optimum oral solid dosage form in terms of formulation design and bioavailability of new pharmaceutical products. In recent years, lipid solutions, emulsions and emulsion pre-concentrates, which can be prepared as physically stable formulations suitable for incorporation of such poorly soluble drugs are gaining attention. Among lipid-based formulations, self-micro-emulsifying formulations with droplet size < 100 nm are capable to improve the oral bioavailability of hydrophobic drugs primarily due to their efficiency in facilitating solubilization and in presenting the hydrophobic drug in solubilized form whereby dissolution process can be circumvented. Self-micro emulsifying drug delivery systems (SMEDDS) are physically stable isotropic mixture which are easy to manufacture and can be filled in soft gelatin capsules and capable to generate a drug containing micro-emulsion with a large surface area upon dispersion in the gastrointestinal tract. The micro sized emulsion will facilitate the absorption of the drug due via intestinal lymphatic pathway and by partitioning of drug into the aqueous phase of intestinal fluids. Some disadvantages are possessed by Conventional SMEDDS which are prepared in a liquid form. So solid SMEDDS (S-SMEDDS) prepared by solidification of liquid/semisolid self-micron emulsifying systems into powders, tablets, pellets etc have gained popularity. In this review, an overview of SMEDDS, their solidification techniques and various factors that potentially affect the oral bioavailability of such drugs are presented.

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KEYWORDS: *Low solubility, Oral bioavailability, Self micro-emulsion*

INTRODUCTION

SMEDDS or Self- Micro emulsifying oil formulations are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents and co-solvents/ surfactants. Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w microemulsions. Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water. Poorly water-soluble drugs that have been formulated as SEDDS or SMEDDS for which an enhanced oral bioavailability has been observed include itraconazole, carvedilol, chloramphenicol, ibuprofen, ketoprofen, tamoxifen, testosterone and tolbutamide. For drug substances that exhibit poor water solubility but sufficient lipophilic properties, it will be beneficial to dose them in a pre-dissolved state, e.g., in a lipid formulation, thereby reducing the energy associated with a solid-liquid phase transition and overcoming the slow dissolution process after oral intake. In self-emulsifying formulations, the formed emulsion increases membrane permeability as a result of surfactant presence and enhances lymphatic absorption (lymphatic transport) due to medium and

long chain oils. These factors may contribute significantly to the better performance of the formulations. [1,2]

The basic difference between self-emulsifying drug delivery systems (SEDDS) also called as self-emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 100 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds which exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time profiles. [3]

ADVANTAGES OF SMEDDS [4]

SMEDDS offer the following advantages;

1. Irritation caused by prolonged contact between the drug and the wall of the GIT can be surmounted by the formulation of SMEDDS as the microscopic droplets formed help in the wide distribution of the drug along the GIT and these are transported quickly from the stomach.
2. Upon dispersion in water, these formulations produce fine droplets with enormous interfacial area due to which the easy partition of the drug from the oil phase into the aqueous phase is possible which cannot be expected in case of oily solutions of lipophilic drugs.
3. SMEDDS are advantageous over emulsions in terms of the stability because of the low energy consumption and the manufacturing process does not include critical steps. Simple mixing equipment is enough to formulate SMEDDS and time required for preparation is also less compared to emulsions.
4. Poor water-soluble drugs which have dissolution rate limited absorption can be absorbed efficiently by the formulation of SMEDDS with consequent stable plasma-time profile. Constant plasma levels of drug might be due to presentation of the poorly soluble drug in dissolved form that bypasses the critical step in drug absorption, that is, dissolution.
5. Along with the lipids, surfactants that are commonly used in the formulation of SMEDDS like Tween 80, Spans, Cremophors (EL and RH40) and Pluronics are reported to have inhibitory action on efflux transporters which help in improving bioavailability of the drugs which are substrates to the efflux pumps. The efflux of paclitaxel from the GIT was found to be inhibited with formulation prepared using surfactant named polysorbate 80.
6. Drugs which have propensity to be degraded by the chemical and enzymatic means in GIT can be protected by the formulation of SMEDDS as the drug will be presented to the body in oil droplets.
7. Microemulsion preconcentrate is advantageous over microemulsion to dispense in the form of liquid filled soft gelatin capsules.
8. SMEDDS are advantageous over SEDDS as the former are less dependent on bile salts for the formation of droplets by which better absorption of the drug is expected compared to SEDDS.
9. Surfactants of high HLB like Tween 80 are reported to increase the permeability of the drug when administered along with the formulation due to the loosening effect of these on tight junctions.

DISADVANTAGES OF SMEDDS [5]

1. Lack of good predicative in-vitro models for appraisal.
2. High surfactant concentration (>30-60%) causes GI irritation.
3. Volatile co-solvents in the traditional definitions move into the shells of soft or hard gelatin capsule bringing about precipitation of lipophilic medications.
4. Lack of good IVIVC correlation and appropriate animal model for in-vivo study.
5. May generate softening or hardening effect on capsule shell, during unit dosage preparation.
6. Dissolution test cannot be completely relied on, because this formulation depends on digestion.
7. Lipid excipients containing unsaturated fatty acids and its derivatives are prone to lipid oxidation. This requires inclusion of lipid soluble antioxidant in capsule formation.
8. Liquid SMEDDS exhibit problems in handling, storage and stability. Thus, formulating solid SMEDDS seems to be a logical solution to address these problems.

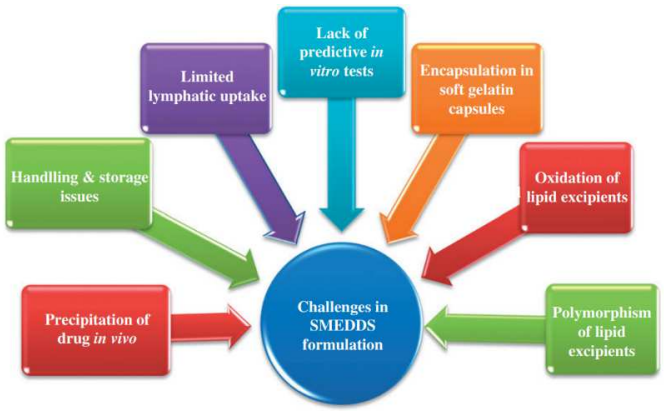

Fig 1: Challenges in SMEDDS formulation

THE EMULSIFICATION PROCESS: [6]

The first observation of a possible spontaneously formed emulsion was made in the 19th century. Self-emulsification is a phenomenon which has been widely exploited commercially in formulations of emulsifiable concentrates of herbicides and pesticides. Concentrates of crop-sprays are to be diluted by the user, such as farmers or house-hold gardeners, allowing very hydrophobic compounds to be transported efficiently. In contrast, SMEDDS, using excipients acceptable for oral administration to humans, have not been widely exploited and knowledge about their physicochemical principles is therefore limited.

Mechanism of Self-Emulsification:

The free energy of the emulsion can be described by the following equation:

$$\Delta G = \sum N \Pi r 2 \sigma$$

Where, ΔG is the free energy, N is the number of droplets, r is the radius of droplets, and σ is the interfacial energy.

From this equation, it is evident that the lower the interfacial energy the lower the free energy. Self-emulsification occurs when the energy involvement in the dispersion is greater than the energy required for the formation of droplets. The free energy of conventional emulsion is very high as high energy is required to form new surface between two immiscible phases like oil and water. Due to high free energy, the emulsion may not be stable and the two phases tend to separate. But in case of SMEDDS, emulsion formation occurs instantaneously because the free energy of the system is very low and sometimes negative due to the presence of flexible interface. On mixing oil and surfactant/cosurfactant mixture with water, up on mild agitation, an interface is formed between two phases. Then, aqueous phase penetrates through interface and gets solubilized within the oil phase up to the solubilization limit. Increased water penetration causes the formation of dispersed liquid crystalline phase. The amount of liquid crystalline phase depends on the surfactant concentration. Upon mild agitation of SMEDDS, water penetration occurs rapidly and leads to the disruption of interface and droplets will be formed. As microemulsions are thermodynamically stable, equilibrium exists within the system although there is continuous exchange of matter between the different phases. Exchange of matter usually occurs in two different ways like fusion of small droplets followed by the fission of larger droplet into small droplets and fragmentation of droplets which later coagulate with other droplets.

FORMULATION COMPONENTS OF SMEDDS [7,8]

- Active pharmaceutical ingredient (Drug)
- Oil
- Surfactant
- Co-surfactant

1. DRUG:

Lipophilicity and dose of the drug are the main criteria to be considered be considered before the development of SMEDDS formulation. Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS. Ideally drug should have low dose, log P> 2 and should not possess extensive first pass metabolism. High melting point drugs with log P values about 2 are poorly suited to SMEDDS. At the other end of the spectrum, lipophilic drugs with log P values greater than 5, are good candidates for SMEDDS.

2. OIL:

The oil represents one of the most important excipients in the SMEDDS formulations not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Modified or hydrolysed vegetable oils have been widely used since these excipients form good emulsification system with a large number of surfactants approved for oral administration and exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semi synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS formulation.

3. SURFACTANT:

A surfactant is needed to adopt self-emulisification property by SMEDDS which is prime process to form microemulsion and it is also helpful to solubilize the hydrophobic drug; in turn the dissolution rate can be improved. The solubilization behaviour of surfactant for the drug gained popularity due to its inhibitory

effect on drug precipitation in vivo. Permeability barrier that is intestinal cell membrane comprised of lipids can be disrupted by surfactant partition; thereby permeability will be enhanced. Although natural surfactants are less toxic, the efficiency of self-emulsification is limited. For spontaneous emulsification, the surfactants are required to be selected with attention to attain ultralow interfacial tension. The selection of surfactant is based on HLB value. The surfactants with high HLB facilitate the formation of O/W microemulsion. Surfactants with hydrophilic nature, that is, HLB value of greater than 12, along with water soluble cosolvents, are used for drugs with relatively low octanol: water partition coefficient to increase the solvent capacity of the formulation and these systems produce very fine droplets of size less than 100 nm with high surfactant concentration. The less toxicity offered by non-ionic surfactants like oleates, polysorbates, polyoxyls, and so forth compared to ionic surfactants allows them to be used more commonly in the formulation of SMEDDS. With commonly used lipids in the formulation of SMEDDS like medium and long chain triglycerides, the non-ionic surfactants like oleates of HLB 11 having unsaturated acyl side chains are more suitable excipients for efficient self-emulsification.

Utility range of surfactants for the formation of stable SMEDDS is about 30–60%. Care should be exercised to minimize the concentration of surfactant as minimum as possible because the use of high concentration of surfactants has disadvantages like GI irritation, decrease in self-emulsification efficiency, and dehydrating effect on soft and hard gelatin capsules (caused by some of the non-ionic surfactants like polysorbates and polyoxyls) with consequent brittleness. At high concentrations of surfactant, GI irritation occurs due to tissue damage and the efficiency of self-emulsification capacity decreases which may be due to the formation of liquid crystalline phase at the interface which in turn is due to viscous nature.

4. CO-SURFACTANT:

The production of an optimum SMEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant / co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again. This process is known as spontaneous emulsification' forms the microemulsion. However, the use of co-surfactant in self-emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SMEDDS, but also to solubilization of the drug in the SMEDDS.

Oils	Surfactants	Co-surfactant / co-solvent
1. Cotton seed oil 2. Soyabean oil 3. Corn oil 4. Sunflower oil 5. Castor oil 6. Sesame oil 7. Labrafac	1. Polysorbate 20 (Tween 20) 2. Polysorbate 80 (Tween 80) 3. Polyoxy-35-castor-oil	1. Transcutol 2. Isopropyl alcohol 3. Ethanol 4. Polyethylene glycol 5. PEG 400

Table 1. Examples of Oils, Surfactants and Co-Surfactants.

FACTORS AFFECTING SMEDDS: [9]

➢ Nature and dose of the drug:

Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately are most difficult to deliver by SMEDDS. The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. As mentioned above if surfactant or co-surfactant is contributing to the greater extent in drug solubilization then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in the solubilising and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could

actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastro-intestinal tract.

➢ **Polarity of the lipophilic phase:**

The polarity of the lipid phase is one of the factors that govern the drug release from the microemulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of micronized for their propensity to inhibit crystallization and, thereby, generate and maintain the supersaturated state for prolonged time periods. A super saturable self-micro emulsifying drug delivery system (S-SMEDDS) of paclitaxel was developed employing HPMC as a precipitation inhibitor with a conventional SMEDDS formulation. In vitro dilution of the S-SMEDDS formulation resulted in formation of a microemulsion, followed by slow crystallization of paclitaxel on standing. This result indicated that the system was supersaturated with respect to paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SMEDDS formulation produced approximately a 10-fold higher maximum concentration (Cmax) and a 5-fold higher oral bioavailability (F ~ 9.5%) compared with that of the orally administered Taxol formulation (F~2.0%) and the SMEDDS formulation without HPMC (F ~ 1%).

➢ **Droplet size and charge:**

Smaller the droplet size and larger the surface area increases absorption and if the droplet is positively charged the drugs can penetrate into the physiological barrier in deep leads to improved bioavailability.

BIOPHARMACEUTICAL ASPECTS OF SMEDDS:[10,11,12,13]

➢ **Effect on rate of gastric emptying:**

Increase in gastric residence time shows the delivery of the drug of it site of action. In particular, it is the lipid component of the food that plays a vital role in the absorption of lipophilic drugs. Lipids in the GI tract provoke delay in gastric emptying, i.e. gastric transit time is increased leading to enhanced oral bioavailability co-administered lipophilic drug. This can be explained by the ability of a high fat meal to stimulate biliary and pancreatic secretions, to decrease metabolism and efflux activity, to increase intestinal wall permeability, and to a prolongation of GIT residence time and transport via lymphatic system. Triglycerides and long chain fatty acids play a major role in prolonging the GIT residence time.

➢ **Effect on Digestion and solubilization of drug:**

The balance between a drug's solubility in the aqueous environment of the gastrointestinal lumen and its permeation across the lipophilic membrane of enterocytes determines its rate and extent of absorption. Following ingestion, of SMEDDS, gastric lipase initiates the digestion of exogenous dietary TG and formulation TG. Simultaneously, the mechanical mixing (propulsion, grinding and retropulsion) of the stomach facilitates formation of a crude emulsion (comprised of aqueous gastric fluid and lipid digestion products). Later in the small intestine, pancreatic lipase together with its cofactor co-lipase203 completes the breakdown of TG to diglyceride, monoglyceride and fatty acid. Pancreatic lipase acts primarily at the sn-1 and sn-3 positions of TG to produce 2-monoglyceride and free fatty acid. The chemical digestion of formulation- or biliary-derived phospholipid (PL) also occurs in the small intestine in which pancreatic phospholipase A2 hydrolyses a single fatty-acid molecule from the sn-2 position of PL to yield lysophosphatidylcholine and fatty acid. The presence of exogenous lipids in the small intestine also stimulates secretion of endogenous biliary lipids, including bile salt (BS), PL and cholesterol from the gall bladder. Previously formed monoglycerides, fatty acids, and lysophospholipid (products of lipid digestion) are subsequently in corporate into a series of colloidal structures, including micelles and unilamellar and multilamellar vesicles in the presence of bile salts. The solubilization and absorptive capacity of the small intestine for lipid digestion products and drugs (D) is significantly enhanced due to these formed lipid metabolites.

➢ **Promotion of intestinal lymphatic transport:**

For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism. Lipids increase the TG-rich lipoproteins which react with drug molecules. Lipoproteins-drug complex enhances intestinal lymphatic transport and leads to changes in drug disposition and finally changes the kinetics of the pharmacological actions of poorly soluble drugs. The effect of structured triglycerides with varying intra molecular structures and chain lengths incorporated into a SMEDDS on the intestinal lymphatic transport and absorption of halofantrine into the blood was investigated. The SMEDDS formulation included 29% w/w structured triglyceride designated as LLL, LML, or MLM (L: long chain fatty acid, C18; M: medium chain fatty acid, C8-10). The MLM and LML micro-emulsions had a similar droplet size of 50 nm. The lymphatic transport of halofantrine,

expressed as the cumulative percentage of the administered dose, after 12 h (mean % dose ± S.E.) was 27.4 ± 1.3 after administration in the LML and 17.9 ± 1.3 in the MLM. The results indicated that the structural formation of the triglyceride initiated a lymphatic transport at a high level. It was therefore hypothesized that medium chain fatty acid enhanced the absorption into the systemic blood circulation whereas long chain fatty acid enhanced the lymphatic transport. Thus, the absorption profile of a drug formulated into a SMEDDS could be manipulated by varying the medium and long chain triglyceride content in the formulation in order to improve the oral bioavailability of highly lipophilic drugs. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly via a reduction in first-pass metabolism. A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicron) and instead may diffuse directly in to the portal supply. Hence in this case, increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs.

- **Effect on intestinal permeability:**

Oil component alters the solubility of the drug in SMEDDS by penetrating into the hydrophobic portion of the surfactant monolayer. Extent of oil penetration varies and depends on the molecular volume, polarity, size and shape of the oil molecule. Overall drug solubility in SMEDDS is always higher than the solubility of drug in individual excipients that combine to form SMEDDS. However, such higher solubility considerably depends on the solubility of drug in oil phase, interfacial locus of the drug and drug-surfactant interactions at the interface. In light scattering experiments, it was observed that oils with small molecular volume act like co-surfactants and penetrate into the surfactant monolayer. This forms thinner polyoxyethylene chains near the hydrophobic core of the micelle disrupting the main locus of the drug solubilization due to which, a higher solubility of drug is not observed. Large molecular volume oils, however, forms a distinct core and do not penetrate effectively into the surfactant monolayer. The locus of drug solubilization was found to be affected by the microstructure and solubility of the drug in the excipients. The locus of drug solubilization was found to be at the interface of micelle for phytosterols whereas the same for cholesterol was found to be between the hydrophobic head groups of surfactant molecules. This is attributed to altered side chain flexibility of phytosterol due to the additional substitution of alkyl side chain compared to cholesterol. In addition to molecular volume and polarity of the oil, drug solubility in oil is affected by physicochemical properties of drug molecule itself. Consideration of BCS classification and Lipinski's rule of 5 for the selection of drug is only useful during initial screening stages. As per BCS classification, some of the acidic drugs are listed in Class II despite having good absorption and disposition as they do not satisfy the requirement of higher solubility at low pH values. Lipinski's rule of 5, on the other hand, holds good only when the drug is not a substrate for the active transporter. This suggests that aqueous solubility and log P alone are not sufficient to predict the solubility of drug in the oil. This further indicates that the solubility of any two drugs with similar log P would not be the same due to their different physicochemical properties.

- **Reduced metabolism and efflux activity:**

In some cases, as shown recently, excipients incorporated in SMEDDS can inhibit both pre-systemic drug metabolism and intestinal efflux mediated by P-gp resulting in an increased oral absorption of drugs. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism. Therefore, uptake of lipophilic drugs formulated as SMEDDS from the GI tract can enhanced due to decrease in the P-gp drug efflux. In addition to a multidrug efflux pump, phase I metabolism by the intestinal Cytochrome P450s is now becoming recognized as a significant factor in oral drug bioavailability.

- **Increase in effective luminal drug solubility:**

The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous billiard lipids including phospholipids (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these Structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.

CONSTRUCTION OF PSEUDO TERNARY PHASE DIAGRAM: [14]

This diagram helps to find out the ratio of water, oil and surfactant/co-surfactant required to form micro emulsion. 100% of the particular component is represented by each corner of diagram. It is prepared to find out micro emulsion region. If formulation contains co-surfactant, it may be studied for micro emulsion region, in different ratio with surfactant as a single pseudo component. The relative amounts of

these three components can be represented in a ternary phase diagram. Effect of change in ratios of the different component on micro emulsion region can be shown by ternary phase diagrams. Each point within the triangle defines a mixture of the three components. These points can be combined to form regions that represent the phase behaviour. Dilution and Water Titration methods as described below can be used to plot Pseudo ternary phase diagrams.

➢ **Dilution Method:**

Each of the oil, surfactant and co-surfactant concentration will range from 10 to 90% (w/w). Total of each of these components in each mixture will always be added to 100%. Microemulsion formation can be evaluated by diluting each mixture with appropriate qty. of water. Droplet size of the emulsions formed can be determined by spectroscopy technique. The area of microemulsion formation in Pseudo ternary phase diagram can be determined for each system.

➢ **Water Titration Method:**

Mixtures of oil, surfactant and co-surfactant can also be titrated with water to prepare pseudo-ternary phase diagrams. Various mixture with oil phase, surfactant and the co-surfactant (S mix) are prepared where ratio of oil and S mix ranges from 9:1 to 1:9. Each mixture is titrated with water with stirring to attain equilibrium. Each mixture is examined (by visual observation) for transparency and further titrated with water until appearance is turbid. Clear samples represents micro emulsion region.

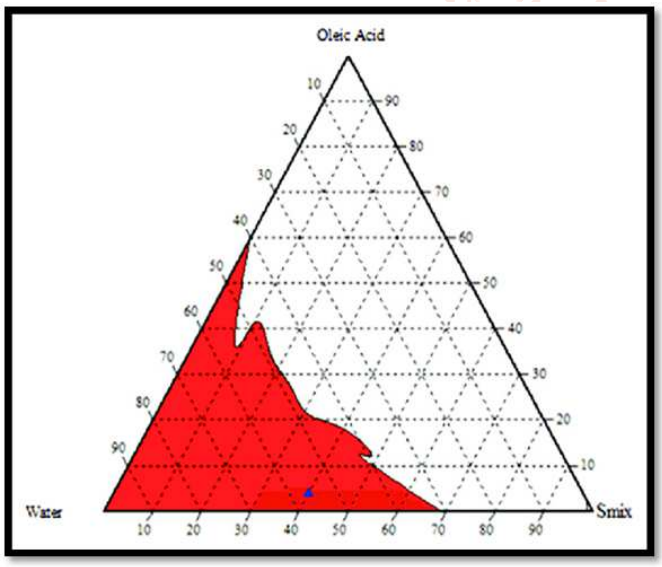

Figure 2: Ternary Phase Diagram

FORMULATION OF SMEDDS: [15]

Upon dilution, the SMEDDS formulation immediately forms a clean dispersion and stays stable. The hydrophobic drug dispersed within the SMEDDS components remains solubilized it is absorbed. Efficient release of the drug from the formula in particular depends on two elements, globule length and polarity of the droplets. In case of oil-in water micro-emulsions, the polarities of oil droplets aren't significant, because the drug included within the oil globules attain the capillaries. The following parameters need to be taken into consideration for the duration of the formula of SMEDDS:

1. Solubility of the drug in various oil, surfactants and co-solvents.
2. Selection of oil, surfactant and co-solvent based at the solubility of the drug, and preparation of the phase diagram.

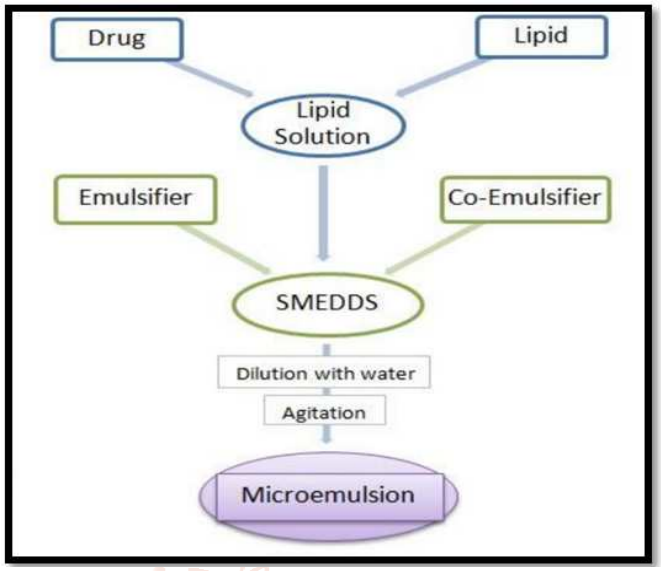

Figure 3 Flow chart for preparation of SMEDDS

EVALUATION OF SMEDDS: [16,17,18,19]

The efficiency of self-micro-emulsification could be estimated by determining the evaluation parameter.

1. Droplet size and particle size measurement:

The particle size of the micro emulsion is determined by photon correlation spectroscopy or SEM (Scanning Electron Microscopy) which can measure sizes between 10 and 5000 nm.

2. Refractive index and percent transmission:

Refractive index and percent transmittance proves the clearness of formulation. The refractive index of the SMEDDS is measured by refractometer and compared with that of water. The percent transmittance of the system is measured at particular wavelength using UV-visible spectrophotometer keeping distilled water as blank, if refractive index of system should be similar to that of water. Formulation showing transmittance >99 percent is transparent in nature.

3. Thermodynamic stability studies:

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation

physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

a) Heating cooling cycle: Six cycles between refrigerator temperature (4ºC) and 45ºC with storage at each temperature of not less than 48 hr is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.
b) Centrifugation: Passed formulations are centrifuged thaw cycles between 21 ºC and +25 ºC with storage at temperature for not less than 48s hr is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.
c) Freeze thaw cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

4. Zeta potential measurement:

Zeta potential for micro emulsion can be determined using a suitable Zeta sizer, in triplicate samples.

5. Determination of self-emulsification time:

The emulsification time of SMEDDS is determined according to USP 2; dissolution apparatus about 2 mg of each formulation are added drop wise to 500 ml purified water at 37°C. Gentle agitation is provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time is assessed visually. This gives the formulator information regarding time lapsed during formulation.

6. Cloud point measurement:

Cloud point determines stability of microemulsion at body temperature. Dilute about 0.5 ml of SMEDDS formulation with 50ml water. Warm the sample at the rate of 0.5º C/min. The temperature when dispersion becomes cloudy is noted as cloud point temperature.

7. Viscosity determination:

Determination of viscosity is important for SMEDDS without dilution. Low-viscous formulations are difficult to handle because of loss of formulation due to flopping around filling nozzle of machine while filling in to capsule shell. This further leads to leaking of capsules and unit to unit weight variation. Viscosity of the SMEDDS formulation can be evaluated by Brookfield viscometer.

8. In Vitro Dissolution Profile:

Drug release from formulation can be evaluated after filling the formulation in a hard gelatin capsule using USP XXIII apparatus I at 100 rpm or USPXXIII apparatus II at 50 rpm or with dialysis method at 37 ± 0.5◦ C. Samples at regular intervals should be withdrawn from the medium and drug content is estimated and compared with the control. The polarity of oil droplet has impact on drug release from the diluted SMEDDS. The higher the polarity, the faster the drug release from the oil droplet into the aqueous phase. Polarity is mainly dependent on the HLB of surfactant, molecular weight of hydrophilic part of the surfactant, and its concentration along with the degree of unsaturation of fatty acid of lipid phase.

9. Dispersibility test:

The efficiency of self-emulsification of oral Nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One millilitre of each formulation is added to 500 ml of water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50rpm provides gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) Nano emulsion having a clear or bluish appearance.

Grade B: Rapidly forming slightly less clear having a bluish-white appearance. Grade C: Fine milky emulsion that forms within 2 min.

Grade D: Dull greyish white emulsion having slightly oily appearance that is slow to emulsify.

Grade E: Formulation exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as Nano emulsion when dispersed in GIT. While formulation falling in Grade C could be recommended for SMEDDS formulation.

SOLID SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (S-SMEDDS):

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, S-SMEDDS have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS. From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self-emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticle technology, and so on). Such

powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient. In the 1990s, S-SEDDS were usually in the form of SE capsules, SE solid dispersions and dry emulsions, but other solid SE dosage forms have emerged in recent years, such as SE pellets/tablets, SE microspheres/nanoparticles and SE suppositories/implants. [20]

SOLIDIFICATION TECHNIQUES FOR TRANSFORMING LIQUID/SEMISOLID SMEDDS TO S-SMEDDS: [21,22,23]

Various solidification techniques are as listed below;

- **Capsule filling with liquid and semisolid self-emulsifying formulations:**

Capsule filling is the simplest and the most common technology for the encapsulation of liquid or semisolid SE formulations for the oral route. For semisolid formulations, it is a four-step process:

1. Heating of the semisolid excipient to at least 20˚C above its melting point.
2. Incorporation of the active substances (with stirring)
3. Capsule filling with the molten mixture.
4. Cooling to room temperature. For liquid formulations, it involves a two-step process: filling of the formulation into the capsules followed by sealing of the body and cap of the capsule, either by banding or by micro-spray sealing.

- **Spray drying:**

Essentially, this technique involves the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers, and solubilization of the mixture before spray drying. The solubilized liquid formulation is then atomized into a spray of droplets. The droplets are introduced into a drying chamber, where the volatile phase (e.g the water contained in an emulsion) evaporates, forming dry particles under controlled temperature and airflow conditions. Such particles can be further prepared into tablets or capsules. The atomizer, the temperature, the most suitable airflow pattern and the drying chamber design are selected according to the drying characteristics of the product and powder specification.

- **Adsorption to solid carriers:**

Free flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and just involves addition of the liquid formulation onto carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or, alternatively, mixed with suitable excipients before compression into tablets. A significant benefit of the adsorption technique is good content uniformity. SEDDS/SMEDDS can be adsorbed at high levels [up to 70% (w/w)] onto suitable carriers.

- **Melt granulation:**

Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a one-step operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent.

- **Melt extrusion/extrusion spheronization:**

Melt extrusion is a solvent-free process that allows high drug loading (60%), as well as content uniformity. Extrusion is a procedure of converting a raw material with plastic properties into a product of uniform shape and density, by forcing it through a die under controlled temperature, product flow, and pressure conditions.

DOSAGE FORM DEVELOPMENT OF S-SMEDDS: [24]

Various dosage forms of S-SMEDDS are as listed below;

1. Dry emulsions
2. Self-emulsifying capsules
3. Self-emulsifying sustained/controlled-release tablets/pellets
4. Self-emulsifying implants
5. Self-emulsifying solid dispersions
6. Self-emulsifying beads
7. Self-emulsifying sustained-release microspheres
8. Self-emulsifying nanoparticles
9. Self-emulsifying suppositories

CONCLUSION:

Self-micro-emulsifying drug delivery systems are recent and effective approach for the augmentation of oral bioavailability of many poor water-soluble drugs provided that the drug should be potent with high lipid solubility. It is well demonstrated that SMEDDS promotes lymphatic delivery of extremely hydrophobic drugs (with high octanol: water partition coefficient) with good solubility (>50 mg/mL) in triglycerides. Faster and enhanced drug release can be attained with smaller droplets which in turn promotes bioavailability. The present review highlighted the developmental steps (solubility studies, construction of pseudo-ternary phase diagrams, and various evaluation tests) involved in obtaining a robust and

stable dosage form. Further research in developing SMEDDS with surfactants of low toxicity and to develop in vitro methods to better understand the in vivo fate of these formulations can maximize the availability of SMEEDS in market.

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